REMARKS/ARGUMENTS

Independent claims 1, 35, and 75 have been amended to recite that the formulation includes 0.04% to 0.06% by weight of solid fluticasone particles. As provided in paragraph [0001] of the published application (i.e., U.S. Publication No. 2004/0209852), Publication No. 2004/0208830 (Ser. No. 10/414,682) has been incorporated by reference in its entirety. Further, the present application is a continuation-in-part of Ser. No. 10/414,682. Support for the recited weight percent can be found at least on paragraph [0033] of Publication No. 2004/0208830 (Ser. No. 10/414,682). The present specification has been amended to explicitly include paragraph [0033] of Publication No. 2004/0208830 (Ser. No. 10/414,682).

Independent claim 1 has also been amended by incorporating the subject matter of claim 3 and to recite that the steroidal anti-inflammatory is fluticasone or a pharmaceutically acceptable salt, ester, enol ether, enol ester, acid, or base thereof. Support for this amendment can be found throughout the application as originally filed.

Dependent claim 10 has been amended to recite about 25 mcg of said steroidal anti-inflammatory.

Claims 71-75 have been amended to correct typographical errors.

No new matter has been entered.

The Currently Claimed Invention

The currently claimed invention comprises a nasal pharmaceutical formulation for the treatment of fungus-induced rhinosinusitis comprising an aqueous suspension of 0.04% to 0.06% by weight of suspended solid fluticasone having a specific suspended solid particle size distribution profile characterized by 5 different micron ratings in combination with an antifungal agent and/or an antiviral agent. These formulations are suitable for intranasal administration to an individual. Accordingly, the recited particle size distributions represent solid particulates of fluticasone suspended in an aqueous medium. By utilizing solid particles of fluticasone, a longer duration for treatment is achieved over formulations wherein an active drug substance is in a dissolved or liquid state. Surprisingly, formulations comprising the claimed particle size

distributions provide increased bioavailability over conventional formulations when administered intranasally.

Claim Objections

The Office has objected to claims 71-74 for the misspelling of "edetate". As such, claims 71-74 have each been amended to correct this typographical error. The Office has objected to claim 75 for misspelling "cidofovir". As such, claim 75 has been amended to correct this typographical error.

Rejections under 35 U.S.C. §112

A.

Claims 1, 3-6, 10-15, 22-25, and 27-30 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement and also for failing to satisfy the enablement requirement. The Office argues that the specification does not provide support or enable solvates or hydrates of fluticasone. As such, independent claim 1 has been amended by deleting "solvates or hydrates". Applicant submits that the current amendment to claim 1 overcomes each of these rejections under 35 U.S.C. §112, first paragraph. Thus, Applicant requests withdrawal of each of these rejections.

B.

Claims 75-76 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The office argues that it is unclear as to the metes and bounds of the Markush group of antiviral agents due to the term "consisting essentially of". As such, independent claim 75 has been amended by deleting the word "essentially". Additionally, claim 76 has been amended by replacing the word "comprising" with "is". Applicant submits that the current amendments to claims 75 and 76 overcome each of these rejections under 35 U.S.C. §112, second paragraph. Thus, Applicant requests withdrawal of each of these rejections.

Rejections under 35 U.S.C. §103

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit ''no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases.'' *Id.* at ___, 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* at ___, 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that '' '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' '' *Id.* at ___, 82 USPQ2d at 1396.

A.

Claims 1, 10-15,and 22-25 and 27-28 stand rejected under 35 U.S.C. §103(a) as being obvious over "FLONASE®" from the online Physician's Desk Reference ("PDR®"), as evidenced by the 199-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) (hereinafter "Lacy") in view of U.S. Patent No. 6,464,958 to Bernini et al. (hereinafter "Bernini").

Applicant submits that each of FLONASE and Bernini fail to teach, suggest, or render predictable each and every element as recited in independent claim 1 or any claims dependent thereon. Specifically, none of the cited references teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the recited particle size distribution characterized by 5 distinct levels; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone in combination with an antifungal agent as recited in independent claim 1.

FLONASE is a 50 mcg of microcrystalline aqueous suspension of fluticasone propioinate. FLONASE can be used for the perennial rhinitis in patients above 12 years of age. See Lacy. As discussed in paragraphs [0053] – [0090] of Publication No. 2004/0208830 (Ser. No. 10/414,682), which was incorporated by reference in its entirety, a controlled study was performed where the fluticasone used in the Dey FP nasal spray was derived from a different source than FLONASE (i.e., the Dey FP nasal spray had a different particle size distribution then FLONASE). The Office acknowledges that Lacy does not teach the currently claimed particle size distributions, but that the particle size distribution is obviated by the teachings of Bernini.

Bernini is primarily directed to a process for preparing aqueous suspensions of drug particles for inhalation into the lungs. Bernini's process includes the following steps: (i) preparing an aqueous solution constituting the carrier and optionally containing wetting agents, surfactants, viscosity-increasing agents, stabilizing agents, isotonicity agents and/or buffers, in a suitable turboemulsifier vessel; (ii) sterilizing the aqueous base inside the same container; (iii) adding, in a sterile environment, one or more active sterile micronised ingredients (i.e. fluticasone dipropionate); and (iv) dispersing all of the ingredients by using the sameturboemulsifier. The resulting aqueous suspensions are intended for nebulisation so that the fluticasone is deposited into the lungs.

However, each of FLONASE as evidenced by Lacy and Bernini fail to teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the recited particle size distribution characterized by 5 distinct levels; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone in combination with an antifungal agent as recited in independent claim 1. As such, each of the cited references, alone

or in combination any combination, fails teach, suggest or render predictable every element currently recited in independent claim 1. As such, Applicant submits that this obviousness rejection has been overcome. Applicants request withdrawal of this rejection

Additionally, Applicant notes that Bernini teaches that if nasal administration is employed, the particle sizes having a higher MMAD than 5-6 microns are required to reach the lungs. Applicant notes that Bernini is completely silent regarding the particle size (e.g. MMAD) necessary for targeting the nasal mucosa. Accordingly, Bernini necessarily fails to provide any teaching regarding a nasal formulation suitable for intranasal administration to target the nasal mucosa. Similarly, Bernini also fails to provide any teaching that would incite one of skill in the art to prepare a formulation utilizing any of the particle size distributions disclosed in the Examples section as a nasal formulation. That said, one skilled in the art would lack a rational basis for modifying the particle size distribution of FLONASE, a nasal formulation, to approach any of the particle size distributions disclosed in Bernini (disclosed for treating the lungs) or alternatively those of the currently claimed invention. In absence of the currently claimed invention, any such proposed modification of FLONASE is devoid of any rational basis. Accordingly, such a proposed modification appears to be motivated by Applicant's currently claimed invention, which is impermissible. Thus, in addition to not teaching each and every claimed element, Applicant submits that the modification of FLONASE by Bernini in the manner proposed is improper. Applicant requests withdraw of this rejection.

B.

Claims 3-6, 29-30 and 35 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference ("PDR®), as evidenced by the 199-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and further in view of U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken").

The Office relies on Osbakken for the teaching of formulations including an antifungal agent or an antibiotic.

FLONASE and Bernini have been discussed above.

Osbakken is directed to compositions having a specific surface tension to yield a liquid aerosol cloud for inhalation having a mass median aerodynamic diameter (MMAD) of between 0.5 and 10 microns. Osbakken teaches adjusting the surface tension of a solution such that it yields a liquid aerosol cloud having an MMAD in a pre-determined range. For example, Osbakken teaches that "this aerosol cloud will have liquid aerosol particles" having certain MMAD ranges. Further, Osbakken stresses the importance of controlling the surface tension of the composition so that the liquid droplets are deposited in the appropriate locations of a patient. See paragraph [0092]. As noted in previous responses, Osbakken is directed to solutions of dissolved active as opposed to suspensions of solid active.

Despite teaching solutions containing both an anti-inflammatory and an antifungal agent, Osbakken fails to cure all of the deficiencies noted in FLONASE, Bernini, and any combination thereof. As such, any combination the Osbakken, FLONASE, and Bernini also fails to teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the recited particle size distribution characterized by 5 distinct levels; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone in combination with an antifungal agent as recited in independent claims 1, 35, or 75. As such, each of the cited references, alone or in combination any combination, fails teach, suggest or render predictable every element currently recited in independent claims 1, 35, and 75 (or any claims dependent thereon). As such, Applicant submits that this obviousness rejection has been overcome. Applicants request withdrawal of this rejection.

C.

Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference ("PDR®"), as evidenced by the 199-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of U.S. Patent No. 6,368,616 to Doi (hereinafter "Doi") and U.S. Patent No. 6,608,054 to Meade (hereinafter "Meade").

The Office relies on Doi for teaching suspensions for nasal applications containing citric acid and EDTA. The Office cites Meade for teaching that sodium edetate and citric acid are known complexing agents.

Doi is generally directed to stabilizing an aqueous suspension of loteprednol etabonate and improving intranasal retention of the active ingredients. Doi is also concerned with the feeling-of-use using thickeners including cellulose derivatives such as methylcellulose, carboxymethylcellulose sodium, hydroxypropylmethylcellulose, etc., synthetic macromolecular compounds such as polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, etc., and saccharides such as sorbitol, mannitol, sucrose, etc.; cationic surfactants including quaternary ammonium salts; anionic surfactants including alkylsulfates; and nonionic surfactants including polysorbate 80, polyoxyethylene hydrogenated castor oil, etc.

Meade is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, neither Doi, Meade, nor any combination thereof cure the aforementioned deficiencies of FLONASE, Bernini, OSbakken, or any combination thereof. As such, any combination the Osbakken, FLONASE, and Bernini also fails to teach, suggest, or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the recited particle size distribution characterized by 5 distinct levels; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone in combination with an antifungal agent as recited in independent claims 1, 35, or 75. Therefore, Doi, Meade, or any combination thereof fail to cure the deficiencies of the FLONASE/Bernini or FLONASE/Bernini/Osbakken. Applicant requests withdrawal of this rejection.

D.

Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference ("PDR®), as evidenced by the 199-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of "Management of Allergic Rhinitis", Nursing Times, 2003, 99(23), Abstract to Walker (hereinafter "Walker") and "Topical Antiviral Agents for Herpes Simplex Virus Infections", Drugs Today, 1998, 34(12), Abstract to Hamuy et al. (hereinafter "Hamuy").

The Office relies on Walker and Hamuy to show that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are will-known anti-viral agents (Hamuy).

Applicant notes, however, that Walker, Hamuy, or the combination of the two cures the deficiencies noted above. In particular, neither of these secondary references teach, suggest or render predictable any of the following: (1) 0.04% to 0.06% by weight of suspended solid fluticasone particles; (2) the recited particle size distribution characterized by 5 distinct levels; and (3) an aqueous suspension of 0.04% to 0.06% by weight fluticasone in combination with an antifungal agent as recited in independent claims 1, 35, or 75. Thus, Applicant requests withdrawal of this rejection.

Unexpected Results

The Office cites paragraph [0086] of serial number 10/414,682, which has been incorporated into the present application by reference, for stating that there was no statistically significant difference between Dey-FP and FLONASE High and Low Dose groups. However, the Office is ignoring the rest of the sentence which provides that the treatment groups behaved similarly, "except for the magnitude of improvement in TNSS." As discussed below, the **Dey FP Low Dose group realized about a 31% improvement in TNSS over that of the FLONASE Low Dose group after 7 days of treatment** and **about a 26% improvement in TNSS over that of the FLONASE Low Dose group after 14 days of treatment.**

Patients who met all criteria were then randomized to 1 of 6 treatment groups:

(1) Dey-FP 50 mcg Low Dose (100 mcg)--1 spray in each nostril daily;

(2) Dey-FP 50 mcg High Dose (100 mcg)--1 spray in each nostril twice daily;

(3) FLONASE Nasal Spray Low Dose (100 mcg)--1 spray in each nostril daily;

(4) FLONASE Nasal Spray High Dose (200 mcg)--1 spray in each nostril daily twice daily;

(5) placebo--1 spray in each nostril once daily; and

(6) placebo--1 spray in each nostril twice daily

The patients from all six groups recorded their Total Nasal Symptom Score (TNSS) consisted of the sum of the 12-hour assessment scores for runny nose, nasal congestion, sneezing, and itchy nose recorded twice daily on the Patient's TNSS Diary card. In figures 1-4 of the present application, the efficacy of the nasal formulations is expressed as the change from baseline (pretreatment) in a composite score of nasal symptoms (e.g. runny nose, sneezing, nasal itching and congestion) referred to as total nasal symptom scores (TNSS). The change from baseline in TNSS scores is expressed in absolute units (rather tan percent change from baseline). The higher the negative value seen in the LS Mean, the greater was the change (improvement) in TNSS.

As depicted in figures 1-4 (LS MEAN as function of Days of treatment), the magnitude of improvement in TNSS for the Dey FP Low Dose group was surprisingly found to be consistently statistically superior to the FLONASE Low Dose group in relieving symptoms of SAR. Applicant notes that the FLONASE Low Dose group did realize some relief, but the magnitude of improvement in TNSS realized by the Dey FP Low Dose group was a vast improvement over the relief provided to the FLONASE Low Dose group. For example, figure 1 shows that after 1 week (7 days) of treatment, the Dey FP Low Dose group realized an LS Mean of approximately -5.9, while the FLONASE Low Dose group merely realized an LS Mean of approximately -4.5. **As such, the Dey FP Low Dose group realized about a 31% improvement in TNSS over that of the FLONASE Low Dose group after 7 days of treatment**. Figure 1 also shows that after 2 weeks (14 days) of treatment, the Dey FP Low Dose group realized an LS Mean ofapproximately -7.8, while the FLONASE Low Dose group merely

realized an LS Mean of approximately -6.2. **As such, the Dey FP Low Dose group realized about a 26% improvement in TNSS over that of the FLONASE Low Dose group after 14 days of treatment.** Applicant submits that one skilled in the art (and one suffering from the symptoms of seasonal allergic rhinitis) would recognize that a 26% to 31% improvement due to the claimed particle size distributions is not merely a minor difference.

Even more unexpected, the Dey FP Low Dose group realized better relief in TNSS than the FLONASE High Dose group. These results were unexpected because the skilled artisan would not have expected the Dey FP Low Dose group to realize improved relief in TNSS over the FLONASE High Dose group, which received double the medicament. As noted above, the only difference between the Dey FP nasal sprays and the FLONASE sprays was the particle size distribution of the fluticasone. **This particular result, surely is a difference in kind rather than one of degree (e.g., Dey FP Low Dose groups received half the active than the FLONASE High Dose group but exhibited a relief in TNSS greater than the FLONASE High Dose group.).**

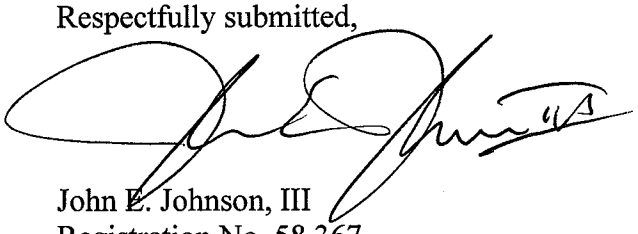
Therefore, the fact that the claimed distributions afford unexpected results provides further evidence of the non-obviousness of the currently claimed invention.

Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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